Response to Comments Received on "A Regulatory Approach for Deriving Trichloroethylene Cancer Potency Estimates for use in the Development of Health Based Remediation Closure Levels"

Introduction and Summary

The Indiana Department of Environmental Management, Office of Land Quality (IDEM) derived draft slope factors for Trichloroethylene (TCE, CAS 79-01-6) and released the technical document supporting that derivation for public comment in January 2006. The TCE technical document, "A Regulatory Approach for Deriving Trichloroethylene Cancer Potency Estimates for use in the Development of Health Based Remediation Closure Levels" (Review Draft), can be found at http://www.in.gov/idem/programs/land/risc/tce_announcement.html (a brief overview of the issues can also be found at this website).

IDEM received comments on the Review Draft through March 17, 2006. IDEM would like to thank those who submitted comments and appreciates the opportunity to address the issues raised. Where similar comments regarding a single central issue were received, IDEM paraphrased the comments and addressed them by category. IDEM believes it has addressed all the comments received.

An overview of the comments reflects that misunderstanding may exist regarding the issues surrounding TCE and use of the proposed non-default TCE slope factor. It appears that the misunderstanding stems from the National Center for Exposure Assessment's (NCEA) release of new science information on the potency of TCE coupled with its adoption of new science policy.

As adequate guidance is not currently available on how to implement the new science and policy, IDEM proposes a new default slope factor to derive Default Closure Levels (DCLs). However, the new default slope factors are not intended to exclude submittals for non-default applications. Users may submit non-default slope factors, commensurate with the state of the science and appropriate guidance, at their own discretion.

The regulatory and science issues surrounding TCE present new and unique challenges, not only to IDEM, but other states and the EPA Regions as well. The TCE issue is especially complicated because NCEA issued new science policy at the same time they issued new toxicity information about TCE potency. The practical implications of the new science policy, rather than the new toxicity information, are really the focus of the current TCE issue. Even though the issues are complex and convoluted, IDEM is required to regulate TCE in a responsible and reasonable manner while being clear and consistent about how choices are made. It is IDEM's intent to communicate

its position as clearly as possible and to provide the reasons certain choices were made.

Essentially, NCEA issued new science policy when it listed a "range" of numerical slope factor values for TCE. Under the new science policy, a user would select a slope factor from within this range based on one of two approaches: either the general application of the slope factor was the key to its use (screening level tables), or site specific exposure variables could be used to derive a site specific slope factor. As a matter of implementation policy, EPA Regions 3, 6, and 9 (the Regions) chose to use the highest or most conservative portion of the range in their screening level tables, while allowing other site specific slope factors for site-specific closure.

In 2004, IDEM, following a commitment to regularly update its DCL tables, chose to use the same system as EPA. That is, IDEM used the high end of the slope factor range in its default closure level tables, while allowing for other slope factors to be used for site-specific applications. However, when working through how to actually evaluate a site-specific slope factor for closure, IDEM discovered that the EPA guidance consistently leads the user to the most conservative portion of the range. The practical implication of this discovery is that users can only select a single slope factor and that slope factor is always the "most conservative." This single conservative value seems inconsistent with the NCEA guidance.

At this point in time IDEM had a number of choices:

- Place the burden on the regulated community to justify site-specific slope factors
- Abandon the EPA new science and new science policy
- Derive independent guidance on how to use a range
- Select the single most representative slope factor value from the range

At first glance, the first option seemed unreasonable, the second option seemed to ignore significant, supported new science, while the third option appeared to offer some resolution. IDEM attempted to derive guidance on how to "use the range" at the 2004 Midwestern States Risk Assessment Symposium. IDEM concluded it was not possible to derive range guidance and decided to use available information to derive a single new default slope factor that could be used in default site closures. IDEM believes the new default slope factor solution is consistent with past practices and agreements it made with the regulated community while taking into consideration the new science. IDEM considers this solution to be an "interim" approach and will re-evaluate its use as EPA develops new policy.

IDEM is aware of the divergent national opinion about how to regulate TCE. As a result of this controversy, IDEM believes it is important to be consistent with past practices when selecting TCE toxicity potency estimates by continuing to follow a process that was agreed upon with the regulated community and the public in 2001.

In the case of TCE, the Regions and other respected science bodies (i.e., Science Advisory Board), have demonstrated considerable support for the new science and policy approach. EPA proposed this approach through the NCEA with the release of "Trichloroethylene Health Risk Assessment: Synthesis and Characterization" (NCEA, 2001). Because there is considerable support for this document and its use is consistent with the process IDEM has followed when deriving potency estimates, IDEM has elected to use the document and derive default slope factors during the interim period. IDEM believes its derived default slope factor values are consistent with agreed upon past practices, while being consistent with the intent of the NCEA (2001) as it has been used by the EPA Regional experts.

IDEM believes that the controversy about TCE is not likely to be resolved in the short term, and new EPA guidance is not likely to be available in that time. The recent release of National Academy of Sciences' (NAS) report "Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues" (2006) while presenting significant guidance to EPA on how to begin sorting through the complex science issues, offers no immediate practical solutions for TCE. NAS is clear about the intent of the document, stating its evaluation focused only on kidney cancer and that this focus was intended to provide a "model" for how other types of cancer should be evaluated. NAS performed only a "qualitative" review of other cancer and non-cancer endpoints. NAS specifically addressed its perspective on evaluating the NCEA (2001), and indicated they neither evaluated this draft health risk assessment, nor assessed the scientific validity of the proposed standards [NCEA, 2001 slope factor range].

NAS did not provide a comprehensive review of the literature on TCE. Instead, NAS focused upon the mode of action information and how it contributes to the hazard characterization of TCE. NAS directs EPA and other Federal agencies to use this information to develop risk assessments for TCE.

In the interim, and after sorting through all the information and the comments, IDEM believes the slope factors proposed in the Review Draft represent the best choice for default toxicity information. Should a user find a site-specific application, it may interpret the science and submit non-default proposals for a slope factor. Note, however, the use of the old, pre- 2004 slope factor information is not an encouraged non-default option. IDEM has studied the use of the old slope factors and finds that this option, as an interim measure, neither addresses the significant body of new science evidence, nor is consistent with the process for deciding toxicity information to which IDEM previously agreed.

Response to Comments

1. Comments re: Use of the Draft 2001 NCEA Document

The 2001 NCEA document should not be used to derive toxicity potency estimates.

The 2001 NCEA document is not legally or scientifically defensible.

The 2001 NCEA document is neither final nor rule and should not be used.

Regions 3, 6 and 9 should not have used the NCEA document to derive toxicity values.

IDEM should return to the TCE toxicity potency estimates it used prior to 2004.

Response: The NCEA (2001) is used by the Regions to set the potency value of the TCE slope factor. Many comments were received requesting that IDEM ignore this document and return to pre-2004 slope factors.

Ignoring the NCEA (2001) would be inconsistent with the process that IDEM has established for selecting slope factors, and would also ignore a large body of science, including expert opinion that there is a disproportionate response in children to TCE and that adjustments should be made to toxicity potency estimates under certain circumstances. IDEM believes it would be irresponsible to ignore either the selection process it agreed to or reputable scientific information and believes it is imperative that the decisions it makes are transparent and consistent.

A broader context on the nature of this issue may be helpful. It is well known that toxicity information changes as new science information becomes available. IDEM has consistently updated toxicity information to remain current. IDEM uses a framework, called a hierarchy, which defines a process for updating and selecting toxicity potency estimates. IDEM, with considerable external input and approval from the regulated community and public, developed the hierarchy for exactly this purpose: selecting carcinogen potency estimates as new information becomes available. The process is described in the Risk Integrated System of Closure Technical Resource Guidance Document (RISC, 2001).

RISC (2001) clearly articulates how IDEM will select the toxicity values it uses to calculate DCLs. RISC (2001) prescribes that toxicity values from certain sources will be selected in a sequential or preferential order. The Regions all publish toxicity information and are a primary source of toxicity potency information in the RISC hierarchy. The Regions updated their toxicity information prior to 2004 using the NCEA (2001).

The Regions are clearly aware of the NCEA's (2001) "Draft" status and the controversy within EPA about how to regulate and define the potency of TCE; yet, they use this document to select toxicity potency estimates. IDEM believes this choice reflects clear support for the document. In addition, Region 10 (2004), OSWER (2002) and the Department of Energy (2006) all cite support for the NCEA (2001) and reference the slope factor

value from NCEA. IDEM believes the use of NCEA (2001) to be well supported by EPA.

Statements regarding whether the Regions should have used the NCEA (2001) or their "right" to do so are not relevant here. The EPA Science Advisory Board (SAB, 2002) in their review of NCEA (2001) clearly supports the new science and science policy that NCEA (2001) advances. The SAB commends EPA [NCEA] for its use of a "range of cancer potency estimates" and for addressing an increased risk to children from TCE and its metabolites. The SAB supports the new science and regards its use of a range of toxicity potency estimates as a "step forward."

Lastly, it should be noted that approximately twenty-five percent (25%) of the compounds in the RISC Default Closure Level Tables reference NCEA (2001) (relying upon the Regions who reference NCEA (2001), and it is common practice for NCEA to issue draft numbers. In fact, according to Cheryl Overstreet who is responsible for the content of the Region 6 Preliminary Remediation Goal tables, "all NCEA values are draft or provisional." (Overstreet, 2006).

IDEM cannot randomly depart from the framework that is defined by its update process. Working outside the framework would require redefining the framework, and that can only be done with external input. As long as the framework process was developed with external input, remains reasonable and is applicable to the task, then it should be used.

2. Comment re: Other States Do Not Use 0.4 (mg/kg-day)$^{-1}$

Other states do not use 0.4 (mg/kg-day)$^{-1}$

Response: Some commenters submitted lists of the slope factors used by certain states. The listed states used smaller slope factors than IDEM (smaller slope factors result in higher clean-up values). Other commenters indicated that the majority of states have not acted on TCE in advance of EPA guidance.

A large number of states have acted upon this issue and have used the NCEA (2001) to quantify their slope factors. In fact, there are a large number of states using more conservative slope factors (higher slope factors and lower clean-up values) than the default values proposed by IDEM. It is well documented that at least the following states use the most conservative slope factors: (0.4 mg/kg-day^-1): AZ, NH, OR, MO, LA, KY, AR, and GA (Dourson et al., 2005). Clearly the fact that these states are acting in advance of further EPA directives reflects support for the NCEA (2001).

3. Comments re: IDEM's Approach to TCE

Non-default approaches can be used to submit justification for a different slope factor

TCE slope factors do have a practical impact

Why does IDEM want to resolve this issue now?

Requirement for IDEM to investigate toxicity (slope factor) information before using it in OLQ Default Closure Level Tables

Response: NCEA (2001) lists a range of numerical values for potency estimates or slope factors, indicating that different slope factors could be selected for different applications. The Regions use the high end of the slope factor range (lowest clean-up values) in their screening level tables and allow site-specific approaches using non-default slope factors from some other portion of the range (Regions, 2006). IDEM investigated the TCE slope factor, read the NCEA (2001) and concluded the regulated community had the option to submit a "non-default" approach using site-specific slope factors.

Prior to beginning work on the Review Draft, IDEM thought that the "non-default" approach taken by the Regions using the NCEA (2001) was sufficient for Indiana. IDEM believed a non-default case could be made for the use of different portions of the range in site-specific closure. However, when IDEM attempted to derive a process to submit non-default approaches, it was discovered that the guidance presented by NCEA (2001) was inadequate, and that other Regional or national guidance on how to submit non-default approaches did not exist (Regions, 2006). IDEM attempted to derive guidance on how to use the range (MSRAS, 2004) and found that was not possible.

At this point IDEM could have used the highest slope factor and simply stated that non-default site-specific slope factors were allowed. However, without adequate guidance on how to submit site-specific slope factors, IDEM felt this option was unreasonable to the regulated community and opted instead to derive a single point default estimate for use in default closure level applications. Because it does not appear that procedures for a default site-specific slope factor approach can reasonably be developed at this time, IDEM is offering interim default point estimates for industrial and residential applications. The single point estimate is selected from within the range and is suitable for default applications.

4. <u>Comment re: Site-Specific Closure Slope Factors</u>

Site-specific closure slope factors are different than RISC Default Closure Level Slope Factors

Response: Until recently, EPA listed a single slope factor for each carcinogen and this single value was used in all applications. Now, when EPA completes a slope factor assessment, it appears it lists a range of slope factors rather than a single value (i.e., vinyl chloride). While non-default approaches under RISC allow the derivation of a new or different slope factor for a given application, it is deemed onerous for those compounds that are not "range" compounds and instead have only a single value listed in IRIS (or NCEA). To deviate from these IRIS/NCEA single point estimates would require substantial justification as these regulatory bodies have considerable expertise.

With the release of the NCEA (2001), EPA signaled a clear change. TCE toxicity estimates were developed using a group(s) of studies and listed as a numerical range (0.02-0.4 mg/kg-day^-1) of slope factors. It was expected that individual slopes within the range would be used differently (supposedly) depending on exposure and other variables. The Regions currently allow this approach, but do not offer guidance on how to accomplish this (Regions, 2006). IDEM thought this approach unreasonable and attempted to develop guidance (MSRAS, 2004). After thorough and careful examination, IDEM concluded it was not realistic to develop guidance on how to use the range. The only existing range guidance NCEA (2001) does not permit the user to do anything else but select the most conservative portion of the range.

IDEM considers it unreasonable to require the use of the highest portion of the range (most conservative closure levels) all the time. It is the Regions' policy that site-specific slope factors are allowed for TCE (Regions, 2006), but that is not the case with the vast majority of compounds. Investigation of the IRIS database clearly reflects a "single" slope factor for the overwhelming majority of compounds. Unless a compound is listed with a slope factor range it would be difficult to justify, establish, and use a range.

5. <u>Comment re: Regions' Allowance of Site-Specific Slope Factors</u>

Regions allow site-specific slope factors

Response: The Regions allow site-specific slope factors for TCE based upon a "range approach," consistent with, and in support of, the use of NCEA (2001). Notwithstanding, the Regions state they have no written guidance on how to use the "range approach." (Regions, 2006).

While TCE is allowed to have site-specific slope factors, it is not reasonable to conclude that all compounds are treated this way. The use of site-specific slopes for TCE is consistent with the NCEA (2001) approach that lists a range of cancer potency information to be applied based on exposure and other factors. This TCE range approach is not inconsistent with the IRIS. There are a few compounds for which IRIS lists a range (i.e., PCBs), and it is reasonable to conclude that for these compounds the Regions may have site-specific slope factors. However, the vast majority of compounds in IRIS have a single slope factor and it is unreasonable to conclude that the Regions would allow a different slope factor to be used at a given site. To do so would refute the IRIS values. Therefore, the vast majority of compounds in IRIS have a single slope factor and the single slope factor listed by the Regions is applicable to screening and site-specific closure.

6. <u>Comments re: Screening Criteria</u>

Screening criteria are not closure levels

Screening levels used by the Regions are not used for the same purpose as the IDEM Default Closure Levels

Response: The intent, application, and use of the Regions' Screening Level Tables are very similar to the IDEM DCLs. Because the Regions call their tables "screening levels" or "Preliminary Remediation Goals" as opposed to the IDEM nomenclature of "Default Closure Levels" does not support the argument that there exists a fundamental difference in application. Similarly, because the Regions' use of language indicating other closure levels are acceptable in site-specific applications does not mean screening levels cannot be used as closure levels.

The purpose of screening level tables is to determine where "further action" is necessary. A health protective level that indicates "no further action is necessary" is, in effect, a "default" closure level. The purpose of IDEM DCLs Tables is to provide clear guidance on widely acceptable closure levels and also, to determine where further action is necessary. IDEM allows site-specific closure levels and considerable guidance is provided on how to determine them (RISC, 2001). The Regions take the same approach. EPA allows sites to be screened out at or below the screening levels, but they allow sites to close at higher "closure levels."

In other words, if the Regions' screening tables are available to "screen out" then by definition they are DCLs. Any potentially responsible party will clean up to screening levels if it is more cost effective than performing a "site-specific risk assessment" justifying higher closure levels. If the screening level is health protective enough to "screen out", then it is considered health protective enough to close. This screening level use is similar to how IDEM uses the "default" closure level. Any party is allowed to seek a higher closure level under RISC, just as they are allowed to clean up to the DCLs if it is more cost effective.

For illustrative purposes, here is an example of a hypothetical clean up site in any of the Regions. The site has some soil areas below the "screening levels" and other areas above screening levels. By definition, the areas below the screening levels would be "screened out" and no further action would be necessary. For the remaining areas above the screening levels the option exists to simply clean up to the screening levels. Here it may be more cost effective to simply remove the soil down to screening levels, rather than do a "risk assessment" justifying a higher clean up level.

7. <u>Comments re: Use of Certain Values</u>

Use of a 0.4 (mg/kg-day)$^{-1}$ slope factor would complicate risk assessments and remedial decisions

Reduction in clean-up values unwarranted

Response: Many states use 0.4 (mg/kg-day)$^{-1}$ as a slope factor (*see* "Policy response 2 to "Other states do not use 0.4 (mg/kg-day)$^{-1}$**"**). As toxicity information changes, it is common practice to update regularly all toxicity information systems. Health protective DCLs are determined based

on toxicity and exposure, not the complexity of remedial actions, decisions or reduction in clean up values.

While IDEM believes at the 10^-5 risk level TCE can be reliably detected in summa canister indoor air sampling, it is not uncommon for health protective levels or DCLs to be below detection limits. Many compounds fall within this category, and it is a common occurrence to find indoor air background levels above health protective levels.

Groundwater is addressed at MCLs, and TCE has an MCL. The MCL will drive the groundwater value, which in turn will drive the migration to groundwater value in all residential settings. In industrial settings the greater of either the health protective level or the MCL will drive groundwater and migration to groundwater.

8. Comment re: NCEA RfDs

IDEM did not evaluate the NCEA RfDs

Response: It is unnecessary to evaluate the NCEA (2001) RfDs. RfDs were not given as a range and NCEA (2001) is clear about the single RfD recommendation. The Regions use the NCEA (2001) recommended value and the use of the Regions' values are consistent with the toxicity potency selection process the regulated community and IDEM agreed to use (RISC, 2001).

9. Comment re: Clean Up Values

Four sets of default closure clean up values make closure onerous

Response: There are three sets of default closure levels in use: the pre-2004 closure levels, the 2004 updates, and the 2006 updates. Updating toxicity information is consistent with the Regions and many other states. IDEM does not believe the nature of the changes to be inconsistent with other regulatory entities. IDEM believes the use of the 2006 updates to be advantageous to the regulated community. The 2006 updates set higher clean up values, and thus, is a benefit rather than a burden.

IDEM will update the DCL tables using the same process outlined in RISC (2001) that was agreed upon with the regulated community.

10. Comment Re: Draft Values

It is not common practice for the Regions to reference Draft values

Response: It should be noted that approximately twenty five percent (25%) of the compounds in the RISC DCLs Tables reference NCEA (2001) (IDEM references the Regions who reference NCEA). IDEM has always had the understanding that all NCEA values were draft and issued only when toxicity information was not available in more authoritarian systems such as IRIS. It has been common practice for NCEA to issue draft numbers and common practice to reference NCEA as a source in the Regions' tables.

IDEM verified this with EPA Region 6's Cheryl Overstreet, who is responsible for the content of the Region 6 PRG tables (including toxicity information). Ms Overstreet stated, "All NCEA toxicity values in their PRG tables are Draft Values. ...NCEA issues the toxicity values as draft values and the memo accompanying them lists them as draft values." (Overstreet, 2006). If the values received from NCEA are considered draft, then NCEA (2001) is no different.

11. Comment Re: Use of Terminology

Use of the term "required" when referencing the process used to select toxicity information for use in IDEM Default Closure Level tables.

Response: The word "required" was used on page 1 of the Review Draft. Specifically, the term was used in the following sentence: "In turn, IDEM following its own hierarchy, required the use of the EPA PRG tables as a source for slope factor data, and also adopted the 0.4 $(mg/kg\text{-}day)^{-1}$ slope factor."

Use of the term "required" was meant to imply that IDEM was trying to follow a process to which the regulated community agreed. IDEM believes it is "required" to be clear and consistent with the decisions it makes.

IDEM understands RISC is a non-rule policy document and cannot be used as a "requirement." The reasons for the use of the hierarchy relate to consistency and transparency in decision making, not to impose as a requirement.

12. Comment Re: Region 9 Screening Criteria

Use of Cal-EPA data in Region 9 Screening Level Tables

Response: The hierarchy process IDEM has indicated it would use when selecting toxicity information indicates the "Regions" will be used. The hierarchy process does not indicate that the preference in the process will be "other state values" or Cal-EPA. Because Region 9 supports the NCEA (2001) by listing its high end slope factor and Regions 3, 6 and 10 do not list any other TCE values, it seems clear the Regions support the NCEA (2001).

The fact that Cal-EPA slope factors are listed in the Region 9 screening level tables does not mean these values are supported for all site closures. There is no indication that the listing of Cal-EPA slope factors in the Region 9 document presents a "given choice." This is consistent with the position Region 9 has taken in supporting the NCEA (2001), i.e., that it will negotiate acceptable site-specific closure levels. How Region 9 intends to accomplish this is unclear: *see* http://www.epa.gov/region09/waste/sfund/prg/whatsnew.htm. Region 9 states, "It is anticipated that there may be interim guidance provided in the future on how best to address TCE contaminated sites so please stay tuned." IDEM is not aware of any guidance (Regions, 2006) indicating how TCE should be addressed on a site specific basis. In general, Cal-EPA toxicity

values are listed in the Region 9 screening level tables as a convenience for use where Cal-EPA values are significantly more protective than Region 9.

Region 9 states on page 9 of "Region 9 PRGs Table 2002 Update" (Region 9, 2006):

> **2.4 "Cal-Modified PRGs"**
> When EPA Region 9 first came out with a Draft of the PRGs table in 1992, there was concern expressed by California EPA's Department of Toxic Substances and Control (DTSC) that for some chemicals the risk-based concentrations calculated using Cal-EPA toxicity values were "significantly" more protective than the risk-based PRGs calculated by Region 9. At an interagency meeting 10 comprised of mostly toxicologists, it was agreed that PRG values are at best order-of-magnitude estimates, so that if we assume a logarithmic scale, then a difference greater than 3.3 (½ log above or below) would be considered a significant difference. Therefore, for individual chemicals where California PRG values are significantly more protective than Region 9 EPA PRGs, Cal-Modified PRGs are included in the Region 9 PRGs table. For more information on Cal-Modified PRGs, the reader may want to contact Dr. Michael Wade in Cal-EPA's Department of Toxic Substances (DTSC) at (916) 255-6653. **Please note that in the State of California, Cal-Modified PRGs should be used as screening levels for contaminated sites because they are more stringent than the Federal numbers** (emphasis original).

13. <u>Comments Re: Adjustments IDEM Made to the Slope Factor</u>

Adjustment of the slope factor to account for early life exposure

Early Life Susceptibility

TCE is not mutagenic; no slope factor adjustment should be made

The SAB did not reach consensus on an additional early life adjustment and should only do so when supported by a quantitative evaluation.

TCE is not a mutagen why did IDEM adjust the slope factors for disproportionate response

Response: Numerous comments were received regarding the adjustment IDEM made to the derived slope factor to address scientific opinion that there is a disproportionate cancer response to TCE in children. Most commenters indicated the reason for slope factor adjustment was that IDEM considered TCE to be a mutagen. IDEM does not make the claim that the justification for the early life adjustment was because TCE is a mutagen, or even that "genotoxicity could not be ruled out."

The following are the four primary reasons for using an adjustment factor for early life susceptibility:

- The SAB (2002) requested, in their review of the NCEA (2001), that an adjustment be made to the slope factor to address the children's cancer

risk issue if the New Jersey Drinking Water Study (Cohn et al. 1994) was eliminated from consideration. As part of the range, it was the only study that addressed a disproportionate cancer response in children.

- The repeated opinion of the SAB (2002) in their review of NCEA (2001) that there is a disproportionate response in children to TCE.
- EPA guidance (2005a) suggesting additional life stage adjustments to slope factors where the data indicate a disproportionate response.
- The SAB request (SAB, 2004) from its review of the EPA Supplemental Guidance for Assessing Susceptibility from Early Life Exposure to Carcinogens (EPA, 2005a) that compounds with an undefined (or not fully characterized) mode of action, have the same default adjustment to the slope factor as mutagens.

IDEM finds these four facts together to be compelling, and so made an adjustment to the derived slope factor.

In its review of the NCEA (2001), the SAB (2002) states in Section 11.2.1, "[t]hus, if EPA were to decide not to include that study [New Jersey Drinking Water, Cohn et al (1994) referencing a disproportionate response in children] in its determination of cancer risk [range], then an adjustment of the cancer slope factor would be needed to address the children's cancer risk issue." IDEM eliminated the Cohn (1994) study from the acceptable studies to derive a slope factor and believes, in view of the SAB direction, that the adjustment is reasonable.

In Section 11.2.2 the SAB states, "[g]enerally, accepted knowledge of the pharmacokinetics and pharmacodynamics of TCE and its metabolites (Fisher, 1989), solvents in general, and many xenobiotics support the conclusion that children as compared to adults, are potentially at greater risk from TCE and its metabolites." It should be noted that in Section 11.2.1 the SAB seemed to be responding directly to increased "carcinogenic" risk from early life exposure as opposed to an independent adjustment to the RfD for children as it did elsewhere.

Comments were received indicating that because TCE was not a mutagen that an early life adjustment was precluded in the EPA 2005a. EPA 2005a does not exempt non-mutagenic carcinogens from early life adjustments. Instead, the EPA 2005a states that the linear low-dose extrapolation approach (without further adjustment) provides adequate health conservatism in the "absence of chemical specific data indicating differential early life susceptibility." To further clarify, EPA states in a letter (EPA, 2004) responding to the SAB (2004) review of the draft 2005 Supplemental Guidance that "[w]hen data are available for a sensitive lifestage, they should be used directly to evaluate risks for that chemical and that lifestage on a case-by-case basis." The SAB review (2002) clearly indicates that lifestage data exist for TCE, and the data indicate an early life adjustment is warranted.

When determining how to make an adjustment IDEM considered the SAB review (2004) of the EPA, 2005a. The SAB (2004) stated,

> "[t]he Review Panel disagrees with [EPA's] conclusion that approaches and data are insufficient at this time to develop guidance on how to address non-mutagenic chemicals with an unknown mode of action. (Tier 3, Fig. 3 of the Supplemental Guidance). The Review Panel believes the data set for the non-mutagenic carcinogens to be qualitatively similar to that for the mutagenic carcinogens, …although the non-mutagenic carcinogens differ widely in mechanism of action, the patterns of effects and the magnitudes of the ratios of juvenile versus adult incidences in the non-mutagenic data set do not differ appreciably from those in the data set for chemicals with a mutagenic mode of action. Therefore, the Panel believes that the Agency should consider the development and application of default adjustment factors for chemicals that are carcinogenic through an unknown mode of action (Tier 3, Fig. 3 of the Supplemental Guidance)."

The SAB (2004) in its review of the EPA 2005a further states, "[t]he Review Panel suggests that the [EPA] reconsider limiting the application of adjustment factors only to mutagenic agents and instead apply a default approach to both mutagenic and to non-mutagenic chemicals for which mode of action remains unknown or insufficiently characterized."

IDEM believes the language in 11.2.1 (SAB, 2002) to be clear and unequivocal regarding the need for an adjustment to the slope factor for early life susceptibility. Respectfully, IDEM submits that the mode of action for TCE carcinogenicity has not been fully characterized (NCEA, 2001; SAB, 2002; EPA 2005b) and that the SAB's (2002) perspective in the review of NCEA (2001) on the need for a slope factor adjustment constitutes a qualified and positive opinion on "clear chemical-specific data indicating differential early life susceptibility."

14. <u>Comments Re: Early Life Adjustment</u>

Early life adjustment is not necessary because TCE metabolic pathways are immature in young children

Response: Comments were received indicating that key TCE metabolic pathways are immature in young children and that the child may not necessarily be at an increased risk. IDEM would agree that Ginsburg et al. (2004) cites evidence that one of the principle TCE metabolic pathways is immature in young children. However, it does not necessarily follow that TCE is not metabolized or that there are no toxic metabolites. The SAB (2002), in their review of NCEA (2001) does not reach this conclusion. When discussing research by Ginsberg et al. (2002) and Hattis et al. (2003), the SAB (2002) states, "[t]his research is described in Appendix B to this report [SAB, 2002] and the authors concluded that the clearance of TCE and its metabolites are reduced in children, as compared to adults. …[T]he panel also notes that there is evidence that the clearance of many TCE metabolites, which are also

toxic, are delayed." The SAB cites references indicating that the clearance of many metabolites, including TCA and TCOH, was delayed.

It also should be noted that increased risk or increased toxic response in children to environmental agents could result from factors other than differences in the TCE metabolism and clearance of TCE metabolites. For instance, Ginsberg et al. (2002) and McCarver (2004) discuss pharmacodymanic (PD) differences in which the sensitivity of rapidly developing tissues and systems may differ from adults. These PD differences are not necessarily given any less weight when determining disproportionate response.

15. <u>Comments Re: IDEM's Use of Studies</u>

IDEM did not discuss why it did not use studies other than the corn oil gavage studies in the use of the model.

IDEM's use of the "Top Down" approach

IDEM should use the inhalation bioassays to derive both inhalation and oral slope factors rather than the corn oil gavage studies

Response: IDEM established that the NCEA (2001) was well supported nationally and consistent with the process IDEM agreed to use. IDEM then developed a mechanism to select a single point estimate using the studies listed in the NCEA (2001). IDEM chose to approach the derivation of a slope factor by starting with the most conservative NCEA studies and analyzing each in turn using pre-selected analysis criteria until IDEM was satisfied the study or studies could be used to develop a single point estimate.

IDEM termed this mechanism the "top down" approach and began with the NCEA document study that yielded the largest, most conservative slope factor, evaluated the reasonableness of its use to derive a single point slope factor and determined whether that study was unsatisfactory. IDEM moved sequentially down the potential hierarchy until IDEM found a study, or series of studies, considered adequate to derive a slope factor.

This approach is transparent in that it gives details on the possible selection of all studies. IDEM's chose this approach because of the uncertainty associated with the body of science information regarding TCE. As stated previously, there is considerable controversy on the mechanisms and potency associated with TCE (EPA, 2005b). TCE is a multi site, multiple species carcinogen with evidence for multiple modes of carcinogenic action, and there is evidence TCE causes a disproportionate response in certain populations (NCEA, 2001; SAB, 2002, EPA, 2005b). The carcinogenicity of TCE and its relevance to humans is well established. TCE is "reasonably anticipated to be a human carcinogen" (NTP, 2002), and the NCEA, 2001 assessment strengthens the case for applicability to humans.

Under EPA's proposed cancer guidelines of 1996, TCE was characterized as "highly likely to produce cancer in humans." (NCEA, 2001). There is general agreement that the MOA and the potency of TCE remain controversial and there is a great deal of uncertainty regarding TCE potency (EPA 2005b). Given the uncertainty, and the links to human cancer response, reasonable caution is warranted, and use of a "top down" approach seems an appropriate regulatory approach.

16. Comment Re: Search of Literature

It is premature for IDEM to issue new guidance without a completed and updated search of the literature to identify significant new studies.

Response: IDEM agrees and has completed an updated search and review of new literature for applicability. It is important to note that review of literature does not always translate into a direct reference in the Review Draft or other IDEM documents addressing TCE.

17. Comment Re: Development of Interim Slope Factors

Interim slope factors should be developed within the context for the EPA 2005 cancer guidelines.

Response: EPA selected the studies used for deriving the Review Draft slope factors. IDEM believes the development of the specific slope factors using these studies is consistent with the EPA Guidelines for Carcinogen Risk Assessment (EPA 2005c). IDEM also believes the slope factors are consistent with the process used to select slope factors described in RISC (2001). Finally, the process used to select a slope factor is consistent with the range established by NCEA (2001).

18. Comment Re: TERA work

TERA work was not peer reviewed

Response: The PBPK model that TERA used was peer reviewed and that peer review can be found at

http://www.tera.org/vera/TCE/TCE%20PBPK%20Peer%20Consultation%20Meeting%20Report%20final.pdf .

IDEM also included a copy of the TERA report "Human Trichloroethylene Cancer Slope Factor Estimation" detailing how the slope factors were modeled in the web posting of the Review Draft. The TERA report was included in order to make modeling assessment transparent and available for review.

19. Comment Re: California's Slope Factor

Why is the slope factor for California lower?

Response: The slope factor for California was established using an averaging approach. In particular, California used this approach with both

inhalation and ingestion studies (Cal EPA, 1999). The slope factors California derived for the ingestion studies were quite similar to the IDEM results for ingestion studies. However, the inhalation studies California used had significantly lower slope factors. When averaged with the ingestion studies, the inhalation studies decreased the overall California slope factor.

IDEM did not use the inhalation studies in deriving the draft slope factor because in its "top down" approach, IDEM first evaluated the ingestion studies which were considered more conservative. Because the ingestions studies met the selection criteria they were used to derive the IDEM draft slope factor. (*see* response to comment 1 under Technical Issues above).

20. <u>Comments Re: Data</u>

It is not valid to use the data from the 1976 NCI or the 1990 study.

Data are not of adequate quality

Presence of epichlorohydrin in 1976 mouse liver studies

Uncertainty exists in the use of the data set

Should not pool data from 1976 and 1990 studies

Response: Many commenters indicated the NCI (1976) study was inappropriate to use for derivation of a slope factor and contended that IDEM should return to pre-2004 values. Please note that previous slope factor values were derived using the 1976 study. Both the 1985 USEPA and the 1999 Cal EPA slope factors used the 1976 study. IDEM believes the 1976 NCI study was also used to establish the NCEA draft values that were the basis of the IDEM pre-2004 DCL table values.

The previous uses of the 1976 NCI study and the reasons for using it in concert with the 1990 NTP study are discussed in the Review Draft beginning at page 8:

> "California had enough confidence in the 1976 (NCI) study to use it, in conjunction with other studies, to derive an oral slope factor for use in its drinking water standard (Cal-EPA, 1999). Support for the 1976 NCI study also comes from its use by the International Agency for Research on Cancer in 1979 to determine that there was limited evidence TCE is carcinogenic in animals (Cal-EPA, 1999). The NTP peer review of the NTP (1990) study categorized the mouse results as "clear and unequivocal" (Lewandowski and Rhomberg, 2005). EPA found the 1976 study (and another study) to be suitable for deriving the 1985 TCE slope factor (EPA, 1985).
>
> As concerns epichlorohydrin, Cal-EPA (1999) found that the epichlorohydrin doses were small compared to the doses that elicited cancer response and that epichlorohydrin appears to initiate tumors at sites by localized tumorigenic

action where it is in direct contact with tissue (such as nasal or forestomach). Cal-EPA (2005) drew the conclusion that the epichlorohydrin was not the cause of the cancer response in the 1976 NCI study. Rhomberg also states that epichlorohydrin causes site of contact tumors (Rhomberg, 2000). Despite a change in dosing regimen in the NCI (1976) study the results have been widely used in the development of regulatory standards (Cal-EPA, 1999; USEPA, 1985). The mouse results from the NTP (1990) were assessed by a peer review group as "clear and unequivocal" (Lewandowski and Rhomberg, 2005). It should also be noted that both studies have been widely used to derive potency estimates using various pharmacokinetic models (Bois, 2000; Rhomberg, 2000)."

There is additional support for IDEM's reliance upon these studies. The SAB concluded that the epidemiology studies suggest the strongest support for liver cancer (2002, page 11). Lewandowski and Rhomberg (2003) support this position by noting that the mouse liver tumor data appear to be the best source for assessing oral exposure to TCE, and that the liver endpoint seen in both mice and humans lends support to the idea that cross-species extrapolation is valid. Lewandowski and Rhomberg (2003) also state that none of the data from the human studies is significantly better than the mouse liver data as a basis for deriving a slope factor. Lewandowski and Rhomberg (2003) support the position of selecting 0.03 $(mg/kg\text{-}day)^{-1}$as a suitable slope factor by comparing it to the Anttila *et al.* (1995) study using a route to route conversion and obtaining slope factor results lower than 0.03 $(mg/kg\text{-}day)^{-1}$."

It is common scientific practice to pool data sets to derive TCE slope factors. USEPA (NCEA, 2001) pooled the 1976 NCI and 1990 NTP data when deriving a range. Many TCE slope factors have been derived using pooled data (Cal-EPA, 1999; EPA, 1985; Cal-EPA, 2005).

Uncertainty exists in all data sets. The variability in the TERA modeled results of the 1976 NCI data and the 1990 NTP data (IDEM, 2005) are considered reasonable (EPA, 1985). The TERA modeled results differed by about a factor of five. By contrast the data Cal-EPA used to derive their oral slope factor varied by a factor 15, more than an order of magnitude (Cal-EPA, 1999). Given that the NCI and NTP studies are accepted within the scientific community, they were used by EPA to derive a range, and they have been widely used by other states and Regions to determine cancer potency, their use here seems reasonable and well supported.

21. <u>Comments Re: Appropriateness of Modeling</u>

DCA

Only TCA was modeled

DCA, rather than TCA may be the TCE metabolite more relevant to tumorigenicity in humans

Response: The method (mechanism) of action (MOA) for the human cancer response to TCE is unknown at this time and considerable controversy exists regarding metabolites, their relationships and MOA. EPA addresses this controversy in considerable detail (EPA2005b; NCEA 2001; SAB, 2002). Because of the controversy, practical issues attendant to deriving a slope factor become centered on a level of confidence that the slope factor is indeed "protective and reasonable." IDEM selected a mechanism to derive a potency estimate believed to be protective, one that considered the state of the regulatory and science information available, and one that was clear and consistent with past and agreed practices.

With the above considerations in mind, IDEM contracted with TERA (2005) to use the PBPK model they helped develop (USAF-EPA, 2004) and selected the studies to be used in the modeling. The model did not address DCA. The reason the model did not address DCA was summarized by the authors (USAF-EPA, 2004) who stated, "[t]here is currently no adequate data available with which to confidently parameterize a description for another metabolite of interest, dichloroacetic acid (DCA)" and "[g]iven the problems with the currently available data, it is not possible to model the production of DCA from TCE with any confidence."

It is IDEM's understanding that the reason the DCA model predictions were not recommended for use in slope factor derivations is that experimental measurements of DCA were uncertain. Since the same information from the previous models was used in the TERA model, it seems the same uncertainty would have existed in previous models (those used in the NCEA analysis).

IDEM explored the practical implications resulting from modeling only TCA and not both, TCA and DCA. At issue is whether the TCA derived TERA (2005) slope factor was representative, reasonable and protective. To accomplish this comparison a simple geometric mean analysis of Table 4-4 of the NCEA (2001) work was reviewed and compared to the TERA (2005) analysis. Table 4-4 (NCEA, 2001) includes both TCA and DCA modeling results (Fisher 2000; Bois, 2000a; Clewell et al, 2000; Bois 2000b) as adapted by Rhomberg, 2000). Since the modeled data from the 1976 NCI and the 1990 NTP is the same for both the TERA and the NCEA analysis, a direct results comparison seems valid. Table 1 indicates the results:

Table 1 Modeling Comparison Oral Slope Factors

Model	Slope factor (geomean) $(mg/kg\text{-}day)^{-1}$	Relative Difference, low to high value
TERA TCA	0.034	5
Fisher TCA	0.16	13

Bois/Fisher TCA	0.022	12
Clewell TCA	0.44	13
Bois/Clewell TCA	0.13	16
Fisher DCA	0.04	14
Clewell DCA	0.003	14
Bois/Clewell DCA	0.026	16
Geomean all DCA	0.014	220
Geomean all TCA	0.12	240
Overall individual values geomean Fisher, Clewell Bois/Fisher, Bois/Clewell	0.048	2201
Cal-EPA	0.013	15

IDEM based its criteria for slope factor selection on the following (IDEM 2005):

- Selected values should be based on the best current understanding of the state of the science concerning TCE toxicity
- Selected values should adequately protect health but should not be overly conservative
- EPA guidance should be followed wherever it is available

Comparing the TERA (2005) modeling results to the NCEA analysis:

- TERA presents a distinguished model development panel that included experts from EPA, academia and the regulated community
- The data set(s) have been widely used and are well supported
- The geomean TERA results are significantly less variable than previous modeled results
- Compared to composite geomean results from NCEA (2001) the geomean TERA slope factor was health protective, well within the range of previously modeled results, and reasonable.

Considerable weight was given to the fact that two of the principal writers for the USAF-EPA harmonized model were Harvey Clewell and Jerry Fisher. Both individuals had developed the models that served as input into the Rhomberg (2000) analysis and the basis of Table 4-4 in the NCEA (2001). *See* the Review Draft for further discussion.

From a regulatory perspective, two key issues are used to guide the decision process: there remains considerable debate over TCE metabolite

MOA(s) and it was not possible for USAF-EPA (2004) to develop modeling for DCA (even though key personnel were involved who had developed previous DCA models). If the experts agreed that DCA could not be modeled, then all that really remains, from a regulatory perspective, is to verify that the geomean from the TCA TERA modeling is as protective as previous DCA modeling. The composite geomeans in Table 1 present that information. Past DCA modeling results indicate a high degree of variability with a geomean range of 0.003 to 0.04 $(mg/kg\text{-}day)^{-1}$. The overall geomean of past DCA modeling is 0.014 $(mg/kg\text{-}day)^{-1}$. If the DCA modeling used in NCEA (2001) is any indicator of potency then the geomean from the TERA modeling is comparable and/or protective. While the TCA geomean from the NCEA past modeling is signficiantly higher, the principal authors of that modeling have agreed on the new USAF-EPA model (as used by TERA) and it would seem the new model would be preferred.

From a regulatory perspective, if the TERA modeling were disregarded then the overall geomean of all the Table 4-4 NCEA (2001) data would be used. This value at 0.048 $(mg/kg\text{-}day)^{-1}$ is comparable to the geomean of the TERA modeling at 0.034 $(mg/kg\text{-}day)^{-1}$. On balance, the geomean of the TERA modeling presents the best choice for a slope factor.

22. <u>Comment Re: Corn Oil Studies</u>

Corn Oil in the oral studies is responsible for the exaggerated response

Response: While IDEM notes the importance of this issue with vinyl chloride, no other referenced regulatory body has raised this issue when deriving a TCE slope factor. Since the studies the regulatory bodies used to derive TCE slope factors received wide support, without consideration for an exaggerated response due to corn oil, IDEM believes this issue must await EPA direction.

23. <u>Comment Re: Over-reliance on Regulatory Decisions</u>

Potential over-reliance on regulatory decisions regarding TCE slope factors

Response: IDEM would agree this is a concern, as the reasons a given regulatory body has for selecting a slope factor are often not readily apparent, especially with cancer potency information from outside the United States. IDEM attempted to investigate the rationale behind the derivation of slope factors from the written material supplied by each entity explaining the derivation. Generally this information was available. Where it was not, or where the reasoning was unclear, IDEM attempted to adjust its perspective.

24. <u>Comment Re: Using 4.8 as a Multiplier</u>

Reconciling the use of 4.8 as some multiplier.

Response: The use of this factor was meant to imply that the Cohn et al. (1994) study did not consider inhalation as a viable route of exposure, and

that attributing total cancer response only to ingestion yields an inaccurate (over) estimation of the slope factor. To give a crude sense of the potential ramification of this oversight, a comparison was made as to how clean up levels are commonly calculated using slope factors and other input into algorithms. When deriving clean up levels for household water, it is common to include both routes of absorption: inhalation and ingestion. When clean-up levels are derived considering only the oral route, assuming the ingestion and inhalation slope factors are equal, then clean up levels are, on average, about 4.8 times higher. IDEM was not trying to imply a direct quantitative difference, only that the difference was likely to be significant. IDEM apologizes for any confusion the use of this term may have caused.

25. <u>Comment Re: Qualitative use of the Cohn Study</u>

Qualitative use of the Cohn et al. (1994) study

Response: The Cohn study was not suitable for a quantitative measure of the dose-response for slope factor determination. However, its use as a qualitative indicator of a disproportionate response is not unreasonable (certainly the SAB (2002) took this position).

In retrospect, IDEM would agree that the use of Cohn et al. (1994) as a quantitative indicator for the degree of disproportionate response is questionable. In large part IDEM attempted to provide a reason for this comparison in the Review Draft by including the following language:

> While there is no direct comparison implied or stated with these two dissimilar methods, and considerable extrapolation must be assumed to compare these two approaches, the results of the Cohn *et al.* (1994) study may give some broad indication of greater sensitivity of young children to the carcinogenic effects of solvents. It should be noted that the reservations about using the Cohn *et al.* (1994) study to develop quantitative estimates of the carcinogenic potency of TCE focus mainly on the uncertainties about the degree of exposure (TCE dose) received by the members and whether the entire carcinogenic response should be attributed to TCE (in lieu of co-exposure to other chemicals). The relative risks for the cancers investigated are not in question.

IDEM has attempted to clearly establish the reasons for supporting an adjustment to the slope factors for a disproportionate response in children in the Comment Response to issue "13" above.

26. <u>Comment Re: Conversion of Rhomberg/Lewandowski Unit Risk Estimate</u>

Conversion of Rhomberg and Lewandowski (2005) unit risk estimate

Response: IDEM converted the unit risk estimate 9×10^{-7} $(ug/m^3)^{-1}$ as given by Rhomberg and Lewandowski (2005) using 20 m^3 air intake, 70 kg

body weight, and 1000 ug/mg to arrive at 0.0032 $(mg/kg\text{-}day)^{-1}$. Any conversion in the Review Draft from an inhalation unit risk estimate listed as per ug/m^3 or $(ug/m^3)^{-1}$ to $(mg/kg\text{-}day)^{-1}$ was converted in a similar manner unless otherwise noted.

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